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EXAMINER
REDDIG, PETER J

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)
Office Action Summary	10/516,558	CHANO ET AL.
	Examiner	**Art Unit**	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on <u>26 July 2007</u>.

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) <u>1-26</u> is/are pending in the application.

    4a) Of the above claim(s) <u>1-3, 11-16 and 18-26</u> is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) <u>4-10 and 17</u> is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on <u>25 January 2005</u> is/are: a)☐ accepted or b)☒ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All   b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>4/8/05; 1/25/05</u>.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application

6)☒ Other: <u>Notice to Comply</u>.

DETAILED ACTION

1.   Applicant's election without traverse of Group II·claims 4-10 and 17, drawn to a nucleic

acid coding for the polypeptide or protein according to claim 1 and the species SEQ ID NO: 3 and

SEQ ID NO: 19 in the reply filed on July 26, 2007 is acknowledged.

2.   Claims 1-26 are pending.

3.   Claims 1-3, 11-16 and 18-26 are hereby withdrawn from further consideration by the

examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

4.   Due to its presence in the prior art SEQ ID NO: 20 will be rejoined for examination.

5.   Claims 4-10 and 17, drawn to a nucleic acid coding for the polypeptide or protein according

to claim 1 and the species SEQ ID NO: 3 and SEQ ID NO: 19 and 20 are currently under

consideration.

Priority

6.   Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have

been placed of record in the file.

It is noted that Examiner has established a priority date of January 30, 2003 for the instant

application, 10/516,558, because the priority of the instantly claimed invention is based on Japanese

applications 2002-161400 and 2002-214978, which have not been translated and the Examiner is

unable to determine the information in the documents.

If Applicant disagrees with any rejection set forth in this action based on examiner's

establishment of a priority date, January 30, 2003 for the instantly claimed application serial

number 10/516,558, Applicant is invited to submit a proper translation of the priority documents

and to point to page and line where support can be found establishing an earlier priority date. If

Applicants choose to file a translation, then the translation must be filed together with a statement

that the translation of the certified copy is accurate, see MPEP 201.15.

Specification/Drawings

7.   The specification and drawings are objected to for improper disclosure of amino acid

sequences without a respective sequence identifier, i.e. SEQ ID NOs: see p. 38, lines 24-26, Fig. 12,

and Table 1. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through

1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer

readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence

listing, as well as any amendment directing its entry into the specification, and a statement that the

content of the paper and computer readable copies are the same and, where applicable, include no

new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the*

appropriate sequences identification numbers in response to this action will be considered non-

responsive.

8.   The disclosure is also objected to because of the following informalities: There is a

hyperlink in the specification at p. 31, line 19. Removal of the "http://" will disable the hyperlink

and obviate this objection.

        Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any
new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this
title.

9.   Claims 4-6, 8, and 10 are rejected under 35 U.S.C. 101 because the claimed invention is

directed to non-statutory subject matter. Claims 4-6, 8, and 10, as written, do not sufficiently

distinguish over the nucleic acids SEQ ID NO: 3, 19, and 20 as they exist naturally because the

claims do not particularly point out any non-naturally occurring differences between the claimed

products and the naturally occurring products. In the absence of the hand of man, the naturally

occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447

U.S. 303, 206 USPQ 193 (1980). In order to obviate the instant rejection, the Examiner suggests

that the claims should be amended to indicate the hand of the inventor, e.g., by insertion of

"isolated" or "purified" provided the support for such an amendment can be identified in the

specification as originally filed. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10.   Claims 5, 10, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite

for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention.

The term "hybridizing/hybridize under stringent conditions" in claims 5, 10, and 17 renders

the claim indefinite. The term " hybridizing under stringent conditions " is not defined by the claim,

the specification provides one non-limiting example of hybridizing under stringent conditions and

thus it cannot be determined what hybridizing conditions are encompassed by the claims.

Claim 9, which depends on claim 1, recites the limitation "the recombinant vector

containing nucleic acid coding for the polypeptide or protein". There is insufficient antecedent

basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11.   Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the

enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are

summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands

states: "Whether undue experimentation is needed is not a single, simple factual determination, but

rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d

1404). The factors to be considered in determining whether undue experimentation is required

include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance

presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the

state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability

of the art, and (8) the breadth of the claims.

Claim 17 is drawn to a pharmaceutical composition for use in treatment of multidrug

resistance that is resistance to treatment with anticancer agents, wherein the pharmaceutical

composition comprises a nucleic acid coding for the polypeptide or protein of claim 1, SEQ ID NO:

3, or a complementary strand thereof, a recombinant vector containing SEQ ID NO: 3, a

transformant that was transformed with the recombinant vector containing SEQ ID NO: 3, or

nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize

under stringent conditions with SEQ ID NO: 3. Given the teaching of the specification as set forth

below, the claims are reasonably interpreted to mean that the pharmaceutical compositions are to be

used for the treatment of multidrug resistance that is resistance to treatment with anticancer agents

by administration of the nucleic acids alone or in a transformant to a patient.

The specification teaches that SEQ ID NO: 3, the human RB1CC1 gene, was identified as a

differentially expressed gene in U2 Osteosarcoma cells and MDR-variant induced cells, see

Example 1, p. 31 and the sequence listing. The specification teaches that the expression of

RB1CC1 inversely correlated with the multidrug resistance gene (MDR1), see Example 3 and Fig.1.

The specification teaches that doxorubicin reduced the expression of RB1CC1 and the

retinoblastoma (RB1) mRNA and overexpression of MDR1 blocked this down regulation, see

Example 5 and Fig. 5. The specification teaches that the expression of RB1CC1 and the RB1

mRNA correlated in six cell lines and leukocytes and in several tissues, see Example 6, 7and Fig. 6,

7. The specification teaches that the introduction of RB1CC1 into cell lines induces the expression

of the RB1 gene and activation of the RB1 promoter, see Example 8 and 9 and Fig. 9 and 10. The

specification teaches that there is a loss of heterozygosity in the RB1CC1 gene in 5 of 7 primary

breast cancer tumors examined, see Example 10 and Fig. 11. The specification teaches that 7

mutations in the RB1CC1 gene were found among 35 primary breast cancer samples analyzed using

PCR and sequencing with the primers of the invention, including SEQ ID NO: 19 and 20, see

Example 11 and 12, Table 2 and Fig. 12. The specification teaches that the combination of primers

set forth in SEQ I D NOs: 19 and 20 in the sequence listing (CC1-S and CC1-AS) were used as

primers for amplification of RB1CC, see p.36, lines 15-18.

The specification teaches that MDR resistance to treatment with anticancer agents is a major barrier to the successful treatments of cancer. While current understanding of factors that contribute to origins of MDR is limited, it is considered that P-glycoprotein that is a product of an MDR-associated gene (MDR1 gene) is involved in several cancers. It is also known that in other cancers expression of P-glycoprotein correlates inversely with emergence and metastasis of the cancer. It is considered that these different effects of P-glycoprotein are subject to suppression by different gene products or conduct different interactions. The identification of genes associated with MDR is essential in order to clarify these phenomena, see Background of Invention.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed and no nexus has been established between the claimed pharmaceutical compositions and treating multidrug resistance that is resistance to treatment with anticancer agents, which reads on cancer therapeutics, because inferred by and inherent in the recitation of a pharmaceutical composition is the in vivo use thereof for the treatment of disease. Given that the only apparent contemplated use for the pharmaceutical composition is drawn to the use of the claimed invention for the treatment of cancer MDR, it is clear that the claimed invention is for use in the treatment of cancer patients who have developed multidrug resistance.

It is noted however, that the art recognizes the unpredictability of developing novel cancer therapeutics. Given the claimed nucleic acid pharmaceutical, it appears that the claims are drawn to a pharmaceutical composition for (1) immunotherapy of MDR upon expression of the encoded protein and (2) treatment of multidrug resistance by gene therapy and the art recognizes the unpredictability of treating a disease by a method of gene therapy.

As drawn to the art of anti-cancer therapy in general, it is noted that Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para.

1) As drawn to anticancer immunotherapy by administration of nucleic acid encoding an antigen, which upon expression of the antigen leads to an immune response against the antigen, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected in the absence of objective evidence demonstrating treatment of multidrug resistance in an appropriate model system in the specification or art of record, that it would be more likely than not that the

claimed SEQ ID NO: 3,or a complementary strand thereof, a recombinant vector containing SEQ

ID NO: 3, a transformant that was transformed with the recombinant vector containing SEQ ID

NO: 3, or a nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which

hybridize under stringent conditions with SEQ ID NO: 3 could be effectively used for the

immunotherapeutic treatment of multidrug resistance without undue experimentation.

2)   As drawn to anticancer gene therapy using administration of recombinant nucleic acids

involving *in vivo* or *ex vivo* methods has not seen any success despite a great deal of work and

resources. Several reviews in the art show that difficulties with vector selection, mode of delivery

and persistence of predictable and effective levels of expression of the protein, created technical

barriers to the practice of gene therapy methods. Verma et al. states that, "[t]he Achilles heel of

gene therapy is gene delivery..." and that, "most of the approaches suffer from poor efficiency of

delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239,

column 3, paragraph 2). Marshall concurs, stating that," difficulties in getting genes transferred

efficiently to target cells- and getting them expressed-remain a nagging problem for the entire

field", and that "many problems must be solved before genetherapy will be useful for more than the

rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and

page 1055, column 1).

Numerous factors complicate the gene therapy art, which have not been shown to be

overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis

of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-W, NY) explains, "the delivery of

exogenous DNA and its processing by target cells requites the introduction of new pharmakinetic

paradigms beyond those that describe the conventional medicines in use today". Eck et al. teaches

that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of

distribution, rate of clearance into the tissues, etc.), the in *vivo* consequences of altered gene

expression and protein function, the fraction taken up by the target cell population, the trafficking of

the genetic material within cellular organelles, the rate of degradation of the DNA, the level of

mRNA produced, the stability of the mRNA produced, the amount and stability of the protein

produced, and the protein's compartmentalization within the cell or its secretory fat, once produced.

These factors differ dramatically based on the vector used, the protein being produced and the

disease being treated (see Eck et al. bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained

gene expressions are, immune responses and the identity of the promoter used to drive gene

expression. Verma et al. teaches, in reference to *ex vivo* methods, that weak promoters produce only

low levels of therapeutically effective protein, and that only by using appropriate enhancer-

promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma

et al., *supra*, page 240, column 2). Verma et al. further warns that, ". . .the search for such

combinations is a case of trial error for a given cell type" (Verma et al., *supra* , page 240, bridging

sentence of columns 2-3). The state of the art is such that no correlation exists between successful

expression of a gene and a therapeutic result (Ross et al. Human Gene Therapy,1996, Volume 7,

pages 1781-1790, see page1789, column 1, first paragraph). Thus, the art at the at the time of filing

clearly establishes that the expectation for achieving a desired therapeutic effect in vivo by

expressing a therapeutic gene using any of the expression constructs known in the art was extremely

low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[although theoretical advantages of human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see section 3. "Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease. More recently, the unpredictability of delivery was further clarified by the tragic setback, in 2002, in the most celebrated clinical trial drawn to the treatment of SCID in children wherein gene therapy led to cancer because of insertional mutagenesis (see Cheek [Nature, 2002, 420:116-118]) wherein the NIH urged all investigators conducting retroviral-mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available (see Attached Letter of January 14, 2003, Exhibit 4).

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment.

The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Given the unpredictability in the arts of cancer therapeutics and gene therapy one of skill in the art would not believe more likely than not that the claimed pharmaceutical composition(s) would function as claimed for treating multidrug resistance without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12.   Claims 4-8 and 17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, does not reasonably provide enablement for a nucleic hybridizing under stringent conditions with SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, a complementary strand to SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, or a nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, wherein a polypeptide expressed by transcription for the nucleic acid is the polypeptide according to claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the

state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability

of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a nucleic hybridizing under stringent conditions with SEQ

ID NO: 3 coding for the polypeptide or protein according to claim 1, a complementary strand to

SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, or a nucleic acid

represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a

nucleic acid set forth in SEQ ID NO: 3, wherein a polypeptide expressed by transcription for the

nucleic acid is the polypeptide according to claim 1.

This means that any nucleic hybridizing under stringent conditions with SEQ ID NO: 3,

complementary strand to SEQ ID NO: 3, or a nucleic acid represented by a base sequence

comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID

NO: 3 can code for a protein or polypeptide according to claim 1, which is a protein that is present

in the nucleus of animal cell and which has transcription factor function and/or a function that can

induce expression of the RB1 gene.

The specification teaches as set forth above.

The specification teaches that the term "nucleic acid and a complementary strand thereof" of

the present invention refers to a nucleic acid set forth in SEQ ID No: 3 or 4 in the sequence listing

that codes for an amino acid sequence set forth in SEQ ID No: 1 or 2 in the sequence listing and the

complementary strand for the nucleic acid, a nucleic acid hybridizing under stringent conditions

with these nucleic acids, and a nucleic acid having a sequence of at least 15 consecutive base

sequence derived from these nucleic acids in which a peptide encoded thereby is capable of binding

with an antibody against the novel protein RB1CC1. The specification teaches that the term

"hybridizing under stringent conditions" refers to, for example, conditions under which a positive

hybridization signal is still observed even after heating at 42°C in a solution of 6X.SSC, 0.5% SDS

and 50% formamide, and washing at 68 °C in a solution of 0.1.XSSC and 0.5% SDS, see [Nucleic

acid] p. 21-22.

It is noted that the definitions of a complementary strand and a nucleic acid hybridizing

under stringent conditions are none limiting and do not limit the claims to nucleic acids that are

completely complementary or hybridize to the full length of SEQ ID NO: 3.

One cannot extrapolate the teachings of the specification to the scope of the claims because

the claims are drawn to nucleic acids that are not the full length SEQ ID NO: 3 and one of skill in

the art would not predict that polypeptide fragments encoded by the nucleic acid fragments of SEQ

ID NO: 3 would predictably be present in the nucleus of an animal cell and have a transcription

factor function and/or induce expression of the RB1 gene because of the unpredictability of protein

biochemistry is well known in the art.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence

encodes a message that determines the shape and function of a protein and that it is the ability of

these proteins to fold into unique three-dimensional structures that allows them to function and

carry out the instructions of the genome and further teaches that the problem of predicting protein

structure from sequence data and in turn utilizing predicted structural determinations to ascertain

functional aspects of the protein is extremely complex. (col. 1, p. 1306). Bowie et al further teach

that while it is known that many amino acid substitutions are possible in any given protein, the

position within the protein's sequence where such amino acid substitutions can be made with a

reasonable expectation of maintaining function are limited. Certain positions in the sequence are

critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting

protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col. 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col. 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col. 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by Pero et al. (US PG Pub 20030105000) who specifically teach in Example 4 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does

not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similarity to Grb 7 on

the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity

or similarity alone cannot be used to predict the function of a protein.

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al, Scott et al.

and Pero et al., but also the limitations and pitfalls of using computational sequence analysis and the

unknown effects of alternative splicing, post translational modification and cellular context on

protein function as taught by Bork, the effects on the function of a protein encoded by SEQ ID NO:

3 by a nucleic hybridizing under stringent conditions with SEQ ID NO: 3, a complementary strand

to SEQ ID NO: 3, or a nucleic acid represented by a base sequence comprising at least 15

consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 can code for a

protein or polypeptide according to claim 1 cannot be predicted. The specification does not teach

the critical residues that are required for the function of the protein encoded by SEQ ID NO: 3,

RB1CC1. Thus given what is known in the art about the unpredictability of the effect of changes of

protein structure on protein function one cannot predict the effect of the claimed unknown and

undefined changes in protein structure would have on the ability of the contemplated nucleic acid

fragments to code for a protein the functions as contemplated in claim 1.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction

needed to enable the invention is inversely related to the amount of knowledge in the state of the

art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA

1970) the amount of guidance or direction refers to that information in the application, as originally

filed, that teaches exactly how to make or use the invention. The more that is known in the prior

art about the nature of the invention, how to make, and how to use the invention, and the more

predictable the art is, the less information needs to be explicitly state in the specification. In

contrast, <u>if little is known in the prior art about the nature of the invention and the art is</u>

<u>unpredictable, the specification would need more detail as how to make and use the invention in</u>

<u>order for it to be enabling.</u> Given only lack of guidance in the specification, no one skilled in the

art would accept the assertion that the claimed invention would function as contemplated or as

claimed based only on the information in the specification and that known in the art at the time the

invention was made.

The specification provides insufficient guidance with regard to these issues and provides no

working examples which would provide guidance to one skilled in the art and no evidence has

been provided which would allow one of skill in the art to predict that the invention will function

as contemplated with a reasonable expectation of success. For the above reasons, it appear that

undue experimentation would be required to practice the claimed invention.

13.   Claims 4-8 and 17 are rejected under 35 USC 112, first paragraph, as lacking an adequate

written description in the specification.

Claims 4-8 and 17 are broadly drawn to complementary strands of SEQ ID NO: 3, nucleic

acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at

least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3.

Although claim 1 requires the protein to have a transcription factor function and/or induce

expression of the RB1 gene the critical residues for these functions have not been identified.

The state of the art is such that it is well know in the art that complementary strands of

nucleic acids include nucleic strands that are less than full length molecules and range from those

that lack significant complementarity to those that are completely complementary to the claimed

polynucleotide in view of the teaching of US Patent No. 5,912,143 that teaches that the term

complementary refers to the natural binding of polynucleotides under permissive salt and

temperature conditions and specifically teaches that complementarity between two single-stranded

molecules may be "partial" or it may be "complete" (col. 5, lines 19-32). It is noted that claim 5 is

drawn to nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3. However, the

specification does not define hybridizing under stringent conditions in a limiting manner and the

claim does not define hybridization conditions, therefore, it is assumed for examination purposes

that hybridizing under stringent conditions include the entire range of stringent conditions from very

low, or permissive to very high stringency and thus the claimed hybridized polynucleotides read on

polynucleotides that range from those that lack significant complementarity to those that are

completely complementary.

Given the above, it is clear that an adequate written description is essential for one of skill in

the art to make and use the claimed invention.

As it is drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119

F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are

relevant to the instant claims. The Federal Circuit addressed the application of the written

description requirement to DNA-related inventions in University of California v. Eli Lilly and Co.,

119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of

an invention involving a chemical genus, like a description of a chemical species, requires a precise

definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter

sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also

stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in <u>Lilly</u> and <u>Enzo</u> were DNA constructs <u>per se</u>, the holdings of those

cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of

complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to

SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of

a nucleic acid set forth in SEQ ID NO: 3, per <u>Lilly</u> by structurally describing a representative

number of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent

conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the

base sequence of a nucleic acid set forth in SEQ ID NO: 3, or by describing "structural features

common to the members of the genus, which features constitute a substantial portion of the genus."

Alternatively, per <u>Enzo</u>, the specification can show that the claimed invention is complete "by

disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or some

combination of such characteristics."

In this case, the specification does not describe complementary strands of SEQ ID NO: 3,

nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid

comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID

NO: 3, in a manner that satisfies either the <u>Lilly</u> or <u>Enzo</u> standards. The specification does not

provide the complete structure of any complementary strands of SEQ ID NO: 3, nucleic acids

hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15

consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, nor does the

specification provide any partial structure of such polypeptides, nor any physical or chemical

characteristics of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO: 3, this does not provide a description of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 that would satisfy the standard set out in Enzo.

The specification also fails to describe complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 by the test set out in Lilly. The specification describes only SEQ ID NO: 3. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14.   Claims 4-6 and 17 rejected under 35 U.S.C. 102(b) as being anticipated by AB059622

(October 11, 2001) as evidenced by Chano et al. (Oncogene, February 14, 2002, 21:1295-1298,

IDS, see exhibit 3 for date) and Exhibits 1 and 2.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment

of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of

an intended use and is not given weight for purposes of comparing the claims with the prior art. The

claims read on the product per se, i. e. SEQ ID NO: 3, a recombinant vector containing SEQ ID

NO: 3, or a transformant transformed with a recombinant vector containing SEQ ID NO: 3.

The claims are drawn to:

3.   A nucleic acid coding for the polypeptide or protein according to claim 1, SEQ ID NO: 3,

or a complementary strand thereof.

5.   A nucleic acid hybridizing under stringent conditions with the nucleic acid according to

claim 3 or the complementary strand thereof.

6.   A nucleic acid represented by a base sequence comprising at least 15 consecutive bases of

the base sequence of a nucleic acid set forth in SEQ ID NO: 3 in the sequence listing or a

complementary strand thereof, wherein a polypeptide expressed by transcription of the nucleic acid

is the polypeptide according to claim 1.

17.   A pharmaceutical composition for use in treatment of multidrug resistance that is resistance

to treatment with anticancer agents, wherein the pharmaceutical composition comprises a nucleic

acid coding for the polypeptide or protein or a complementary strand thereof according to claim 1

(SEQ ID NO: 3), a recombinant vector containing the nucleic acid, a transformant that was transformed with the recombinant vector, listing which hybridize under stringent conditions with the nucleic acid.

AB059622 teaches a sequence that is identical to SEQ ID NO: 3, see Exhibit 1. Given the identity of the prior art molecule to the instantly claimed molecule, it inherently would encode a polypeptide with the properties set forth for the protein of claim 1.

Exhibit 2 teaches that AB059622 was publicly available October 11, 2001.

Further, Chano et al. teach the protein encoded by AB059622, RB1CC1, can induce the expression of the RB1 gene, see Abstract, Fig. 2 and Fig.4.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15.   Claims 7-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Chano et al. (Oncogene, February 14, 2002, 21:1295-1298, IDS, see Exhibit 3 for date) as evidenced by Exhibit 2.

The claims are drawn to:

7. A recombinant vector containing the nucleic acid according to claim 4.

8. A transformant that was transformed with the recombinant vector according to claim 7.

9. A method for producing the polypeptide or protein according to claim 1, comprising a step of culturing the transformant with the recombinant vector containing nucleic acid coding for the polypeptide or protein.

10. Nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing, which hybridize under stringent conditions with the nucleic acid according to claim 4 or the complementary strand thereof.

17.   A pharmaceutical composition for use in treatment of multidrug resistance that is

resistance to treatment with anticancer agents, wherein the pharmaceutical composition

comprises nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing

which hybridize under stringent conditions with SEQ ID NO: 3.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment

of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of

an intended use and is not given weight for purposes of comparing the claims with the prior art. The

claims read on the product per se, i.e. nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the

sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

It is also noted that although the claims are being examined as drawn to SEQ ID NO: 3 and

variants thereof, the claims does not limit the nucleic acid in the recombinant vector to being the

full length SEQ ID NO: 3.

AB059622 teaches a sequence that is identical to SEQ ID NO: 3, see Exhibit 2

Chano et al. teach a transforming a recombinant vector containing the cDNA encoding the

RB1CC1 protein into K562 and Jurkat cell lines, see Fig. 4. Chano et al. teach the protein encoded

by AB059622, RB1CC1, can induce the expression of the RB1 gene, see Abstract, Fig.2 and Fig.4.

Chano et al. teach that SEQ ID NO: 19 and SEQ ID NO: 20 were used in RT-PCR amplification of

RB1CC1, see Fig. 3, Primers CC1S and CC1AS.

The method of the prior art comprises the same method steps as claimed in claimed 9, that

is, comprising a step of culturing the transformant with the recombinant vector containing nucleic

acid coding for the polypeptide or protein according to claim 1, thus the claimed method is

anticipated because the method will inherently be a method for producing the polypeptide or protein

according to claim 1, See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference

does not specifically state that the method is a method for producing the polypeptide or protein

according to claim 1, the claimed method appears to be the same as the prior art method, absent a

showing of unobvious differences. The office does not have the facilities and resources to provide

the factual evidence needed in order to establish that the method of the prior art does not possess the

same material, structural and functional characteristics of the claimed method. In the absence of

evidence to the contrary, the burden is on the applicant to prove that the claimed method is different

from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d

1252, 195 USPQ 430 (CCPA).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness

rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth
> in section 102 of this title, if the differences between the subject matter sought to be patented and the prior
> art are such that the subject matter as a whole would have been obvious at the time the invention was made
> to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be
> negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966), that are applied for establishing a background for determining obviousness under 35 U.S.C.

103(a) are summarized as follows:

1.   Determining the scope and contents of the prior art.

2.   Ascertaining the differences between the prior art and the claims at issue.

3.   Resolving the level of ordinary skill in the pertinent art.

4.   Considering objective evidence present in the application indicating obviousness or

nonobviousness.

This application currently names joint inventors. In considering patentability of the claims

under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the

contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

invention dates of each claim that was not commonly owned at the time a later invention was made

in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C.

102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16.   Claims 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over

AB059622 (October 11, 2001), in view of Mensink et al (British J. Haematol. (August 1998)

102:768-774) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536).

The claims are drawn to:

10. Nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing, which

hybridize under stringent conditions with the nucleic acid according to claim 4 or the

complementary strand thereof.

17.   A pharmaceutical composition for use in treatment of multidrug resistance that is

resistance to treatment with anticancer agents, wherein the pharmaceutical composition

comprises nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing

which hybridize under stringent conditions with SEQ ID NO: 3.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment

of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of

an intended use and is not given weight for purposes of comparing the claims with the prior art. The

claims read on the product per se, i.e. nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the

sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

AB059622 (October 11, 2001) teach SEQ ID NO: 3 as set forth above.

AB059622 does not teach the particular primers of SEQ ID NO: 19 and 20.

Mensink teaches primer selection, "Using the Primer Express software program (Perkin-

Elmer, Foster City, Calif. Demo version 1.0 ppd) we designed PCR primers for the amplification of

cDNA derived from the BCR-ABL transcript and PBGD transcript (page 769, column 2)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to use the method of Mensink to produce primers selected from the sequences

of AB059622 since Mensink expressly teaches primer selection using commercially available

software for BCR-ABL detection from the BCR-ABL published sequences and since AB059622

provide such published sequences for the software program to analyze.

In the recent court decision KSR International Co. v. Teleflex Inc., the U.S. Supreme court

determined that "[w]hen there is a design need or market pressure to solve a problem and there are a

finite number of identified, predictable solutions, a person of ordinary skill has good reason to

pursue the known options within his or her technical grasp. If this leads to the anticipated success, it

is likely the product not of innovation but of ordinary skill and common sense. In that instance the

fact that a combination was obvious to try might show that it was obvious under §103." KSR

International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)

Since the claimed primers simply represent structural homologs of SEQ ID NO: 3 that are

derived from sequences suggested by the prior art as useful for primers for SEQ ID NO: 3 and

would predictably be within the technical grasp of one of ordinary skill in the art to make, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

16.   No claims allowed.
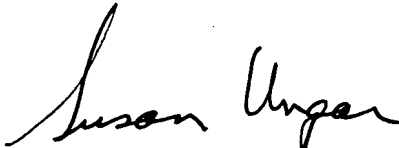
17.   Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig
Examiner
Art Unit 1642

PJR

Exhibit 1

AB059622
LOCUS   AB059622   6636 bp   mRNA   linear   PRI 10-JUL-2002
DEFINITION   Homo sapiens RBICC mRNA for Rb1-inducible coiled coil protein,
               complete cds.
ACCESSION   AB059622
VERSION   AB059622.1 GI:16040976
KEYWORDS   .
SOURCE   Homo sapiens (human)
  ORGANISM   Homo sapiens
               Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
               Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
               Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Chano,T., Ikegawa,S., Kontani,K., Okabe,H., Baldini,N. and Saeki,Y.
  TITLE   Identification of RB1CC1, a novel human gene that can induce RB1 in
               various human cells
  JOURNAL   Oncogene 21 (8), 1295-1298 (2002)
  PUBMED   11850849
REFERENCE   2
  AUTHORS   Chano,T., Ikegawa,S., Saito-Ohara,F., Inazawa,J., Mabuchi,A.,
               Saeki,Y. and Okabe,H.
  TITLE   Isolation, characterization and mapping of the mouse and human
               RB1CC1 genes
  JOURNAL   Gene 291 (1-2), 29-34 (2002)
  PUBMED   12095676
REFERENCE   3 (bases 1 to 6636)
  AUTHORS   Chano,T.
  TITLE   Direct Submission
  JOURNAL   Submitted (10-APR-2001) Tokuhiro Chano, Shiga University of Medical
               Science, Department of Clinical Laboratory Medicine; Seta,
               Tsukinowa, Otsu, Shiga 520-2192, Japan
               (E-mail:chano@belle.shiga-med.ac.jp, Tel:81-77-548-2600(ex.2600),
               Fax:81-77-548-2407)
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                     /chromosome="8"
                     /cell_line="U-2 OS"
                     /cell_type="osteosarcoma"
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     CDS   525. .5309
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```
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            FIKHYREWAGALVKDGKRLYEAEKSKRESFGKLFRKSFLRNRLFRGLDSWPPSFCTQK
            PRKFDCELPDISLKDLQFLQSFCPSEVQPFLRVPLLCDFEPLHQHVLALHNLVKAAQS
            LDEMSQTITDLLSEQKASVSQTSPQSASSPRMESTAGITTTTSPRTPPPLTVQDPLCP
            AVCPLEELSPDSIDAHTFDFETIPHPNIEQTIHQVSLDLDSLAESPESDFMSAVNEFV
            IEENLSSPNPISDPQSPEMMVESLYSSVINAIDSRRMQDTNVCGKEDFGDHTSLNVQL
            ERCRVVAQDSHFSIQTIKEDLCHFRTFVQKEQCDFSNSLKCTAVEIRNIIEKVKCSLE
            ITLKEKHQKELLSLKNEYEGKLDGLIKETEENENKIKKLKGELVCLEEVLQNKDNEFA
            LVKHEKEAVICLQNEKDQKLLEMENIMHSQNCEIKELKQSREIVLEDLKKLHVENDEK
            LQLLRAELQSLEQSHLKELEDTLQVRHIQEFEKVMTDHRVSLEELKKENQQIINQIQE
            SHAEIIQEKEKQLQELKLKVSDLSDTRCKLEVELALKEAETDEIKILLEESRAQQKET
            LKSLLEQETENLRTEISKLNQKIQDNNENYQVGLAELRTLMTIEKDQRISELISRHEE
            ESNILKAELNKVTSLHNQAFEIEKNLKEQIIELQSKLDSELSALERQKDEKITQQEEK
            YEAIIQNLEKDRQKLVSSQEQDREQLIQKLNCEKDEAIQTALKEFKLEREVVEKELLE
            KVKHLENQIAKSPAIDSTRGDSSSLVAELQEKLQEEKAKFLEQLEEQEKRKNEEMQNV
            RTSLIAEQQTNFNTVLTREKMRKENIINDLSDKLKSTMQQQERDKDLIESLSEDRARL
            LEEKKKLEEEVSKLRSSSFVPSPYVATAPELYGACAPELPGESDRSAVETADEGRVDS
            AMETSMMSVQENIHMLSEEKQRIMLLERTLQLKEEENKRLNQRLMSQSMSSVSSRHSE
            KIAIRDFQVGDLVLIILDERHDNYVLFTVSPTLYFLHSESLPALDLKPGEGASGASRR
            PWVLGKVMEKEYCQAKKAQNRFKVPLGTKFYRVKAVSWNKKV"
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ORIGIN

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   Query Match              100.0%;   Score 6636;  DB 5;   Length 6636;
   Best Local Similarity    100.0%;   Pred. No. 0;
   Matches 6636;  Conservative     0;  Mismatches     0;  Indels     0;  Gaps     0;


Qy        1 GTCGACAATAACAAACCAAGCCGCGGCGGTGTCCGCGGCCCTGCCGAGCCCTCGGCGTTG 60
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        1 GTCGACAATAACAAACCAAGCCGCGGCGGTGTCCGCGGCCCTGCCGAGCCCTCGGCGTTG 60

Qy       61 CCTCAGAATCCCCCAGTCGCCTGGGCCCCTCGGCTCTGACAGGCCGCGGCCTTCTGTCCC 120
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       61 CCTCAGAATCCCCCAGTCGCCTGGGCCCCTCGGCTCTGACAGGCCGCGGCCTTCTGTCCC 120

Qy      121 CCGGCCCCAGACCCAGAGCCGAGGGGCCTGCTCGCGTCCTTGTCCGCCCGGACCCCTCCC 180
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      121 CCGGCCCCAGACCCAGAGCCGAGGGGCCTGCTCGCGTCCTTGTCCGCCCGGACCCCTCCC 180

Qy      181 TGCCTCCTAGAGTTCGGGGCCGCGGCGGGCGGGCGCCCGGGACGCCGGCGGTTGTGTCGG 240
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      181 TGCCTCCTAGAGTTCGGGGCCGCGGCGGGCGGGCGCCCGGGACGCCGGCGGTTGTGTCGG 240

Qy      241 CTTAGCGGTGCCGAATGGGCGGTTGGTAACCGCTGCCGAGGACTAGGCGGCGGCGGAAGA 300
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      241 CTTAGCGGTGCCGAATGGGCGGTTGGTAACCGCTGCCGAGGACTAGGCGGCGGCGGAAGA 300

Qy      301 TGGTGCCGGGGGGTCGCTGGCTCTGCTGCTGCCGCCGGCGAAGGAGGAGGCGTTGCCGGTT 360
            |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        301  TGGTGCCGGGGGTCGCTGGCTCTGCTGCTGCCGCCGGCGAAGGAGGAGGCGTTGCCGGTT  360

Qy        361  TTCTGAGTTTAACCAGTAATGCCATTCAGTTGCCAATCTCAAGCAAAGCAAACATAAGCC  420
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361  TTCTGAGTTTAACCAGTAATGCCATTCAGTTGCCAATCTCAAGCAAAGCAAACATAAGCC  420

Qy        421  AGTTTTAATCTACTTTTTAAGAAAAGTGGTAGTCCTTTTCACAGTGCCTGACGTAACTGT  480  -
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421  AGTTTTAATCTACTTTTTAAGAAAAGTGGTAGTCCTTTTCACAGTGCCTGACGTAACTGT  480

Qy        481  ATCAGAGGGTGAGGTATAAGCTCACAGAATTCAGATAAATCATCATGAAGTTATATGTAT  540
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481  ATCAGAGGGTGAGGTATAAGCTCACAGAATTCAGATAAATCATCATGAAGTTATATGTAT  540

Qy        541  TTCTGGTTAACACTGGAACTACTCTAACATTTGACACTGAACTTACAGTGCAAACTGTGG  600
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541  TTCTGGTTAACACTGGAACTACTCTAACATTTGACACTGAACTTACAGTGCAAACTGTGG  600

Qy        601  CAGACCTTAAGCATGCCATTCAAAGCAAATACAAGATTGCTATTCAACACCAGGTGCTGG  660
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601  CAGACCTTAAGCATGCCATTCAAAGCAAATACAAGATTGCTATTCAACACCAGGTGCTGG  660

Qy        661  TGGTCAATGGAGGAGAATGCATGGCTGCAGATCGAAGAGTGTGTACCTACAGTGCTGGGA  720
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661  TGGTCAATGGAGGAGAATGCATGGCTGCAGATCGAAGAGTGTGTACCTACAGTGCTGGGA  720

Qy        721  CGGATACAAATCCAATTTTTCTTTTTAACAAAGAAATGATCTTATGCGATCGTCCACCTG  780
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721  CGGATACAAATCCAATTTTTCTTTTTAACAAAGAAATGATCTTATGCGATCGTCCACCTG  780

Qy        781  CTATTCCTAAAACTACCTTTTCGACAGAAAATGACATGGAAATAAAAGTTGAAGAATCTC  840
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781  CTATTCCTAAAACTACCTTTTCGACAGAAAATGACATGGAAATAAAAGTTGAAGAATCTC  840

Qy        841  TTATGATGCCTGCAGTTTTTCATACTGTTGCTTCAAGGACACAGCTTGCATTGGAAATGT  900
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841  TTATGATGCCTGCAGTTTTTCATACTGTTGCTTCAAGGACACAGCTTGCATTGGAAATGT  900

Qy        901  ATGAAGTTGCCAAGAAACTTTGTTCTTTTTGTGAAGGTCTTGTACATGATGAACATCTTC  960
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901  ATGAAGTTGCCAAGAAACTTTGTTCTTTTTGTGAAGGTCTTGTACATGATGAACATCTTC  960

Qy        961  AACACCAAGGCTGGGCTGCAATCATGGCCAACCTGGAGGACTGTTCAAATTCATACCAAA  1020
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961  AACACCAAGGCTGGGCTGCAATCATGGCCAACCTGGAGGACTGTTCAAATTCATACCAAA  1020

Qy       1021  AGCTACTTTTCAAGTTTGAAAGTATTTATTCAAATTATCTGCAGTCCATAGAAGACATCA  1080
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021  AGCTACTTTTCAAGTTTGAAAGTATTTATTCAAATTATCTGCAGTCCATAGAAGACATCA  1080

Qy       1081  AGTTAAAACTTACTCATTTAGGAACTGCAGTTTCAGTAATGGCCAAGATTCCACTGTTGG  1140
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081  AGTTAAAACTTACTCATTTAGGAACTGCAGTTTCAGTAATGGCCAAGATTCCACTGTTGG  1140
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Qy   1141 AGTGCCTAACCAGACATAGTTACAGAGAATGTTTGGGAAGACTGGATTCTTTACCTGAAC 1200
          |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1141 AGTGCCTAACCAGACATAGTTACAGAGAATGTTTGGGAAGACTGGATTCTTTACCTGAAC 1200

Qy   1201 ATGAAGACTCAGAAAAAGCTGAGACGAAAAGATCCACTGAACTGGTGCTCTCCTGATA 1260
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1201 ATGAAGACTCAGAAAAAGCTGAGACGAAAAGATCCACTGAACTGGTGCTCTCCTGATA 1260

Qy   1261 TGCCTAGAACAACTAACGAATCTTTGTTAACCTCATTTCCCAAGTCAGTGGAACATGTGT 1320
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1261 TGCCTAGAACAACTAACGAATCTTTGTTAACCTCATTTCCCAAGTCAGTGGAACATGTGT 1320

Qy   1321 CCCCAGATACCGCAGATGCTGAAAGTGGCAAAGAAATTAGGGAATCTTGTCAAAGTACTG 1380
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1321 CCCCAGATACCGCAGATGCTGAAAGTGGCAAAGAAATTAGGGAATCTTGTCAAAGTACTG 1380

Qy   1381 TTCATCAGCAAGATGAAACTACGATTGACACTAAAGATGGTGATCTGCCCTTTTTTAATG 1440
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1381 TTCATCAGCAAGATGAAACTACGATTGACACTAAAGATGGTGATCTGCCCTTTTTTAATG 1440

Qy   1441 TCTCTTTGTTAGACTGGATAAATGTTCAAGATAGACCTAATGATGTGGAATCTTTGGTCA 1500
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1441 TCTCTTTGTTAGACTGGATAAATGTTCAAGATAGACCTAATGATGTGGAATCTTTGGTCA 1500

Qy   1501 GGAAGTGCTTTGATTCTATGAGCAGGCTTGATCCAAGGATTATTCGACCATTTATAGCAG 1560
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1501 GGAAGTGCTTTGATTCTATGAGCAGGCTTGATCCAAGGATTATTCGACCATTTATAGCAG 1560

Qy   1561 AATGCCGTCAAACTATTGCCAAACTTGATAATCAGAATATGAAAGCCATTAAAGGACTTG 1620
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1561 AATGCCGTCAAACTATTGCCAAACTTGATAATCAGAATATGAAAGCCATTAAAGGACTTG 1620

Qy   1621 AAGATCGGCTCTACGCCCTGGACCAGATGATTGCTAGCTGTGGCCGACTGGTGAATGAAC 1680
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1621 AAGATCGGCTCTACGCCCTGGACCAGATGATTGCTAGCTGTGGCCGACTGGTGAATGAAC 1680

Qy   1681 AGAAAGAGCTTGCTCAGGGATTTTTAGCTAATCAGAAGAGAGCTGAAAACTTAAAGGATG 1740
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1681 AGAAAGAGCTTGCTCAGGGATTTTTAGCTAATCAGAAGAGAGCTGAAAACTTAAAGGATG 1740

Qy   1741 CATCTGTATTACCTGATTTATGCCTGAGTCACGCAAATCAGTTGATGATTATGTTGCAAA 1800
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1741 CATCTGTATTACCTGATTTATGCCTGAGTCACGCAAATCAGTTGATGATTATGTTGCAAA 1800

Qy   1801 ATCATAGAAAACTGTTAGATATTAAGCAGAAGTGTACCACTGCCAAACAAGAACTAGCAA 1860
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1801 ATCATAGAAAACTGTTAGATATTAAGCAGAAGTGTACCACTGCCAAACAAGAACTAGCAA 1860

Qy   1861 ATAACCTACATGTCAGACTGAAGTGGTGTTGCTTTGTAATGCTTCATGCTGATCAAGATG 1920
          |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db   1861 ATAACCTACATGTCAGACTGAAGTGGTGTTGCTTTGTAATGCTTCATGCTGATCAAGATG 1920

Qy   1921 GAGAGAAGTTACAAGCTTTGCTCCGCCTCGTAATAGAGCTGTTAGAAAGAGTCAAAATTG 1980
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db    1921 GAGAGAAGTTACAAGCTTTGCTCCGCCTCGTAATAGAGCTGTTAGAAAGAGTCAAAATTG 1980

Qy    1981 TTGAAGCTCTTAGTACAGTTCCTCAGATGTACTGCTTAGCTGTTGTTGAGGTTGTAAGAA 2040
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    1981 TTGAAGCTCTTAGTACAGTTCCTCAGATGTACTGCTTAGCTGTTGTTGAGGTTGTAAGAA 2040

Qy    2041 GAAAAATGTTCATAAAACACTACAGGGAGTGGGCTGGTGCTTTAGTCAAAGATGGAAAGA 2100
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2041 GAAAAATGTTCATAAAACACTACAGGGAGTGGGCTGGTGCTTTAGTCAAAGATGGAAAGA 2100

Qy    2101 GATTATATGAAGCAGAAAAATCAAAAGGGAATCCTTTGGGAAATTATTTAGGAAGTCTT 2160
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2101 GATTATATGAAGCAGAAAAATCAAAAGGGAATCCTTTGGGAAATTATTTAGGAAGTCTT 2160

Qy    2161 TTTTAAGAAATCGTCTGTTTAGGGGACTGGACTCCTGGCCCCCTTCCTTTTGTACTCAAA 2220
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2161 TTTTAAGAAATCGTCTGTTTAGGGGACTGGACTCCTGGCCCCCTTCCTTTTGTACTCAAA 2220

Qy    2221 AGCCTCGAAAGTTTGACTGTGAACTTCCAGATATTTCATTAAAAGATTTACAGTTTCTGC 2280
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2221 AGCCTCGAAAGTTTGACTGTGAACTTCCAGATATTTCATTAAAAGATTTACAGTTTCTGC 2280

Qy    2281 AATCATTTTGTCCTTCGGAAGTTCAGCCATTCCTCAGGGTTCCCTTACTTTGTGACTTTG 2340
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2281 AATCATTTTGTCCTTCGGAAGTTCAGCCATTCCTCAGGGTTCCCTTACTTTGTGACTTTG 2340

Qy    2341 AACCTCTACACCAGCATGTACTTGCTCTACATAATTTGGTAAAAGCAGCACAAAGTTTGG 2400
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2341 AACCTCTACACCAGCATGTACTTGCTCTACATAATTTGGTAAAAGCAGCACAAAGTTTGG 2400

Qy    2401 ATGAAATGTCACAGACCATTACAGATCTACTGAGTGAACAAAAGGCATCTGTGAGCCAGA 2460
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2401 ATGAAATGTCACAGACCATTACAGATCTACTGAGTGAACAAAAGGCATCTGTGAGCCAGA 2460

Qy    2461 CATCCCCACAGTCTGCTTCTTCACCAAGGATGGAAAGTACAGCAGGAATTACAACTACTA 2520
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2461 CATCCCCACAGTCTGCTTCTTCACCAAGGATGGAAAGTACAGCAGGAATTACAACTACTA 2520

Qy    2521 CCTCACCGAGAACTCCTCCACCACTGACTGTTCAGGATCCCTTATGTCCTGCAGTTTGTC 2580
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2521 CCTCACCGAGAACTCCTCCACCACTGACTGTTCAGGATCCCTTATGTCCTGCAGTTTGTC 2580

Qy    2581 CCTTAGAAGAATTATCTCCAGATAGTATTGATGCACATACGTTTGATTTTGAAACTATTC 2640
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2581 CCTTAGAAGAATTATCTCCAGATAGTATTGATGCACATACGTTTGATTTTGAAACTATTC 2640

Qy    2641 CCCATCCAAACATAGAACAGACTATTCACCAAGTTTCTTTAGACTTGGATTCATTAGCAG 2700
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2641 CCCATCCAAACATAGAACAGACTATTCACCAAGTTTCTTTAGACTTGGATTCATTAGCAG 2700

Qy    2701 AAAGTCCTGAATCAGATTTTATGTCTGCTGTGAATGAGTTTGTAATAGAAGAAAATTTGT 2760
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    2701 AAAGTCCTGAATCAGATTTTATGTCTGCTGTGAATGAGTTTGTAATAGAAGAAAATTTGT 2760
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Qy     2761 CGTCTCCTAATCCTATAAGTGATCCACAAAGCCCAGAAATGATGGTGGAATCACTTTATT 2820
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     2761 CGTCTCCTAATCCTATAAGTGATCCACAAAGCCCAGAAATGATGGTGGAATCACTTTATT 2820

Qy     2821 CATCAGTTATCAATGCGATAGACAGTAGACGAATGCAGGATACAAATGTATGTGGTAAGG 2880
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     2821 CATCAGTTATCAATGCGATAGACAGTAGACGAATGCAGGATACAAATGTATGTGGTAAGG 2880

Qy     2881 AGGATTTTGGAGATCATACTTCTCTGAATGTCCAGTTGGAAAGATGTAGAGTTGTTGCCC 2940
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     2881 AGGATTTTGGAGATCATACTTCTCTGAATGTCCAGTTGGAAAGATGTAGAGTTGTTGCCC 2940

Qy     2941 AAGACTCTCACTTCAGTATACAAACCATTAAGGAAGACCTTTGCCACTTTAGAACATTTG 3000
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     2941 AAGACTCTCACTTCAGTATACAAACCATTAAGGAAGACCTTTGCCACTTTAGAACATTTG 3000

Qy     3001 TACAAAAAGAACAGTGTGACTTCTCAAATTCATTAAAATGTACAGCAGTAGAAATAAGAA 3060
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3001 TACAAAAAGAACAGTGTGACTTCTCAAATTCATTAAAATGTACAGCAGTAGAAATAAGAA 3060

Qy     3061 ACATTATTGAAAAAGTAAAATGTTCTCTGGAAATAACACTAAAAGAAAAACATCAAAAAG 3120
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3061 ACATTATTGAAAAAGTAAAATGTTCTCTGGAAATAACACTAAAAGAAAAACATCAAAAAG 3120

Qy     3121 AACTACTGTCTTTAAAAAATGAATATGAAGGTAAACTTGACGGACTAATAAAGGAAACTG 3180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3121 AACTACTGTCTTTAAAAAATGAATATGAAGGTAAACTTGACGGACTAATAAAGGAAACTG 3180

Qy     3181 AAGAGAATGAAAACAAAATTAAAAAATTGAAGGGAGAGTTAGTATGCCTTGAGGAGGTTT 3240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3181 AAGAGAATGAAAACAAAATTAAAAAATTGAAGGGAGAGTTAGTATGCCTTGAGGAGGTTT 3240

Qy     3241 TACAAAATAAAGATAATGAATTTGCTTTGGTTAAACATGAAAAAGAAGCTGTAATCTGCC 3300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3241 TACAAAATAAAGATAATGAATTTGCTTTGGTTAAACATGAAAAAGAAGCTGTAATCTGCC 3300

Qy     3301 TGCAGAATGAAAAGGATCAGAAGTTGTTAGAGATGGAAAATATAATGCACTCTCAAAATT 3360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3301 TGCAGAATGAAAAGGATCAGAAGTTGTTAGAGATGGAAAATATAATGCACTCTCAAAATT 3360

Qy     3361 GTGAAATTAAAGAACTGAAGCAGTCACGAGAAATAGTGTTAGAAGACTTAAAAAAGCTCC 3420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3361 GTGAAATTAAAGAACTGAAGCAGTCACGAGAAATAGTGTTAGAAGACTTAAAAAAGCTCC 3420

Qy     3421 ATGTTGAAAATGATGAGAAGTTACAGTTATTGAGGGCAGAACTTCAGTCCTTGGAGCAAA 3480
            ||||||||||||||||||||||||||||||||||||||||||||||φ||||||||
Db     3421 ATGTTGAAAATGATGAGAAGTTACAGTTATTGAGGGCAGAACTTCAGTCCTTGGAGCAAA 3480

Qy     3481 GTCATCTAAAGGAATTAGAGGACACACTTCAGGTTAGGCACATACAAGAGTTTGAGAAGG 3540
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     3481 GTCATCTAAAGGAATTAGAGGACACACTTCAGGTTAGGCACATACAAGAGTTTGAGAAGG 3540

Qy     3541 TTATGACAGACCACAGAGTTTCTTTGGAGGAATTAAAAAAGGAAAATCAACAAATAATTA 3600
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db    3541 TTATGACAGACCACAGAGTTTCTTTGGAGGAATTAAAAAAGGAAAATCAACAAATAATTA 3600

Qy    3601 ATCAAATACAAGAATCTCATGCTGAAATTATCCAGGAAAAAGAAAAACAGTTACAGGAAT 3660
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3601 ATCAAATACAAGAATCTCATGCTGAAATTATCCAGGAAAAAGAAAAACAGTTACAGGAAT 3660

Qy    3661 TAAAACTCAAGGTTTCTGATTTGTCAGACACGAGATGCAAGTTAGAGGTTGAACTTGCGT 3720
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3661 TAAAACTCAAGGTTTCTGATTTGTCAGACACGAGATGCAAGTTAGAGGTTGAACTTGCGT 3720

Qy    3721 TGAAGGAAGCAGAAACTGATGAAATAAAAATTTTGCTGGAAGAAAGCAGAGCCCAGCAGA 3780
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3721 TGAAGGAAGCAGAAACTGATGAAATAAAAATTTTGCTGGAAGAAAGCAGAGCCCAGCAGA 3780

Qy    3781 AGGAGACCTTGAAATCTCTTCTTGAACAAGAGACAGAAAATTTGAGAACAGAAATTAGTA 3840
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3781 AGGAGACCTTGAAATCTCTTCTTGAACAAGAGACAGAAAATTTGAGAACAGAAATTAGTA 3840

Qy    3841 AACTCAACCAAAAGATTCAGGATAATAATGAAAATTATCAGGTGGGCTTAGCAGAGCTAA 3900
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3841 AACTCAACCAAAAGATTCAGGATAATAATGAAAATTATCAGGTGGGCTTAGCAGAGCTAA 3900

Qy    3901 GAACTTTAATGACAATTGAAAAAGATCAGCGTATTTCCGAGTTAATTAGTAGACATGAAG 3960
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3901 GAACTTTAATGACAATTGAAAAAGATCAGCGTATTTCCGAGTTAATTAGTAGACATGAAG 3960

Qy    3961 AAGAATCTAATATACTTAAAGCTGAATTAAACAAAGTAACATCTTTGCATAACCAAGCAT 4020
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    3961 AAGAATCTAATATACTTAAAGCTGAATTAAACAAAGTAACATCTTTGCATAACCAAGCAT 4020

Qy    4021 TTGAAATAGAAAAAAAACCTAAAAGAACAAATAATTGAACTGCAGAGTAAATTGGATTCAG 4080
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    4021 TTGAAATAGAAAAAAAACCTAAAAGAACAAATAATTGAACTGCAGAGTAAATTGGATTCAG 4080

Qy    4081 AATTGAGTGCTCTTGAAAGACAAAAAGATGAAAAAATTACCCAACAAGAAGAGAAATACG 4140
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    4081 AATTGAGTGCTCTTGAAAGACAAAAAGATGAAAAAATTACCCAACAAGAAGAGAAATACG 4140

Qy    4141 AAGCTATTATCCAGAACCTTGAGAAAGACAGACAAAAATTGGTCAGCAGCCAGGAGCAAG 4200
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    4141 AAGCTATTATCCAGAACCTTGAGAAAGACAGACAAAAATTGGTCAGCAGCCAGGAGCAAG 4200

Qy    4201 ACAGAGAACAGTTAATTCAGAAGCTTAATTGTGAAAAAGATGAAGCTATTCAGACTGCCC 4260
           |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy    4381  GCTTAGTTGCTGAACTTCAAGAAAAGCTTCAGGAAGAAAAAGCTAAGTTTCTAGAACAAC  4440
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Qy    4441  TTGAAGAGCAAGAAAAAAGAAAGAATGAAGAAATGCAAAATGTTCGAACATCTTTGATTG  4500
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Qy    4861  AAGAAAATATTCATATGTTGTCTGAAGAAAAACAGCGGATAATGCTGTTAGAACGAACAT  4920
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Qy    5101  CTTTATATTTTCTACATTCAGAGTCTCTACCTGCCCTGGATCTCAAACCAGGTGAGGGTG  5160
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Exhibit 2

LOCUS   AB059622   6636 bp   mRNA   linear   PRI 11-OCT-2001.

DEFINITION   Homo sapiens RBICC mRNA for Rb1-inducible coiled coil protein,

             complete cds.

ACCESSION　　AB059622

VERSION　　　AB059622.1　GI:16040976

KEYWORDS　　　.

SOURCE　　　　Homo sapiens (human)

　ORGANISM　　Homo sapiens

　　　　　　　　Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;

　　　　　　　　Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE　　1　(bases 1 to 6636)

　AUTHORS　　Chano,T., Kontani,K., Ikegawa,S., Okabe,H., Baldini,N. and Saeki,Y.

　TITLE　　　Cloning of a novel Rb1-inducible gene, RBICC

　JOURNAL　　Unpublished

REFERENCE　　2　(bases 1 to 6636)

　AUTHORS　　Chano,T.

　TITLE　　　Direct Submission

　JOURNAL　　Submitted (10-APR-2001) Tokuhiro Chano, Shiga University of Medical

　　　　　　　　Science, Department of Clinical Laboratory Medicine; Seta,

　　　　　　　　Tsukinowa, Otsu, Shiga 520-2192, Japan

　　　　　　　　(E-mail:chano@belle.shiga-med.ac.jp, Tel:81-77-548-2600(ex.2600),

　　　　　　　　Fax:81-77-548-2407)

FEATURES　　　　　　　　Location/Qualifiers

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3661 taaaactcaa ggtttctgat ttgtcagaca cgagatgcaa gttagaggtt gaacttgcgt

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3781 aggagacctt gaaatctctt cttgaacaag agacagaaaa tttgagaaca gaaattagta

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3901 gaactttaat gacaattgaa aaagatcagc gtatttccga gttaattagt agacatgaag
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3961  aagaatctaa tatacttaaa gctgaattaa acaaagtaac atctttgcat aaccaagcat

4021  ttgaaataga aaaaaaccta aaagaacaaa taattgaact gcagagtaaa ttggattcag

4081  aattgagtgc tcttgaaaga caaaaagatg aaaaaattac ccaacaagaa gagaaatacg

4141  aagctattat ccagaacctt gagaaagaca gacaaaaatt ggtcagcagc caggagcaag

4201  acagagaaca gttaattcag aagcttaatt gtgaaaaaga tgaagctatt cagactgccc

4261  taaaagaatt taaattggag agagaagttg ttgagaaaga gttattagaa aaagttaaac

4321  atcttgagaa tcaaatagca aaaagtcctg ccattgactc taccagagga gattcttcaa

4381  gcttagttgc tgaacttcaa gaaaagcttc aggaagaaaa agctaagttt ctagaacaac

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4501  cggaacaaca gaccaatttt aacactgttt taacaagaga gaaaatgaga aaagaaaaca

4561  taataaatga tcttagtgat aagttgaaaa gtacaatgca gcaacaagaa cgggataaag

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4681  aagaagaagt cagtaagttg cgcagtagca gttttgttcc ttcaccatat gtagctacag

4741  ccccagaact ttatggagct tgtgcacctg aactcccagg tgaatcagat agatccgctg

4801  tggaaacagc agatgaagga agagtggatt cagcaatgga gacaagcatg atgtctgtac

4861  aagaaaatat tcatatgttg tctgaagaaa aacagcggat aatgctgtta gaacgaacat

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5101  ctttatattt tctacattca gagtctctac ctgccctgga tctcaaacca ggtgagggtg

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5221  aagccaaaaa ggcacaaaac agatttaaag ttcctttggg gacaaagttt tacagagtga

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5341  ttttttttctg atttgtcctg cagtgctcat tcatcactcc aaaaacagca ggccatcttt

5401  ttatgcaaaa gtcagcgtga caatatactt cactggtgta catcgtttac tttttaactg

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5701 aaatcagtat cagaatactt gcactcttta acacattctt tataaaatgt ataaattatt

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6541 tatgtatatc taatagtaca aaatggaata aacatcatag tgtatagaaa actgaatttg

6601 acaagttaat gaataaatga acaaatgatt tcaaaa
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Exhibit 3
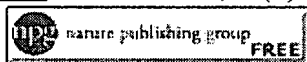
Identification of RB1CC1, a novel human gene that can induce RB1 in various human cells.

Chano T, Ikegawa S, Kontani K, Okabe H, Baldini N, Saeki Y.

Department of Basic Science for Health and Nursing, Shiga University of Medical Science,

Tsukinowa-cho, Otsu, Shiga 520-2192, Japan. chano@belle.shiga-med.ac.jp

Multidrug resistance to anti-cancer agents (MDR) is a major barrier to successful cancer treatment. Current knowledge about genes that contribute to MDR is limited, however, and its mechanisms remain unclear. To identify genes involved in MDR, we performed differential display analysis and isolated a novel human gene, RB1CC1 (RBI-inducible Coiled-Coil 1). The 6.6-kb RB1CC1 cDNA encodes a putative 1594-amino-acid protein that contains a nuclear localization signal, a leucine zipper motif and a coiled-coil structure. Western blot analysis and immunocytochemical staining with anti-RB1CC1 antibody showed that endogenously expressed RB1CC1 protein localized to the nucleus. In MDR variants of human osteosarcoma cells, RB1CC1 expression increased in response to doxorubicin-induced cytotoxic stress and remained elevated for the duration of drug treatment. RB1CC1 expression levels correlated closely with those of RB1 (retinoblastoma 1) in cancer cell lines as well as in various normal human tissues. Moreover, introduction of wild-type RB1CC1 significantly induced RB1 expression in human leukemic cells. These data suggest that RB1CC1 may be a key regulator of RB1 gene expression.

Publication Types:

- Research Support, Non-U.S. Gov't

APPLICATION NO. /CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/516,558	01/25/2005	Tokuhiro Chano	3190-070

EXAMINER
Peter Reddig, Ph.D.

ART UNIT	PAPER
1642	

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification discloses amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NO: see p. 38, lines 24-26, Fig. 12, and Table 1. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

If a complete reply has not been submitted by the time period set in the accompanying Office action has expired, this application will become abandoned under 37 CFR 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned Applicant is requested to return a copy of the

attached Notice to Comply with the reply.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (http://ww.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual-ePAVE)

2. Mailed to

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Commissioner for Patents

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Alexandria, VA 22313-1450

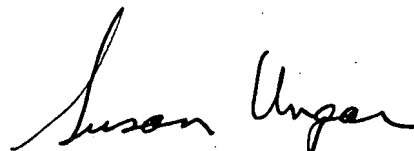3.Hand Carry, Federal Express, United Parcel Service or other delivery service to:

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Reddig whose telephone number is 571-272-9031. The examiner can normally be reached on M-F 8:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley can be reached on 571-272-0898.

Peter Reddig, Ph.D.
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

	Application No.	Applicant(s)
Notice to Comply	10/516,558	Chano et al.
	Examiner	Art Unit	
	Peter Reddig	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The disclosure is lacking numerous sequence identifiers and sequence ID numbers, see the section titled "Sequence Listing" in the accompanying First Office Action on the Merits.

Applicant Must Provide:
☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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